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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/371,354	08/10/1999	STEPHEN DONOVAN	17310	9137

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EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	//

DATE MAILED: 02/25/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/371,354	Applicant(s) DONOVAN, STEPHEN	
	Examiner Bridget E. Bunner	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7,9,10,12,13,15-17 and 35-38* is/are pending in the application.

4a) Of the above claim(s) *12,13,35 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,9,10,15-17,37 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *7,9,10,12,13,15-17 and 35-38* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 05 December 2001 (Paper No. 10) has been entered in full. Claims 8, 11, 14, 18, and 28-34 are cancelled, claims 7, 9, and 15-17 are amended, and claims 37-38 are added.

This application contains claim 12-13 and 35-36 drawn to an invention nonelected with traverse in Paper No. 5 (18 May 2001). A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 7, 9-10, 15-17, and 37-38 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objection to the specification at pg 3 of the previous Office Action (Paper No. 6, 05 July 2001) is *withdrawn* in view of the amended title (Paper No. 10, 05 December 2001).

2. The objection to claim 8 at pg 3-4 of the previous Office Action (Paper No. 6, 05 July 2001) is *withdrawn* in view of the cancelled claims (Paper No. 10, 05 December 2001).

3. The rejection of claims 28-34 under 35 U.S.C. § 112, second paragraph at pg 7 of the previous Office Action (Paper No. 6, 05 July 2001) is *withdrawn* in view of the cancelled claims (Paper No. 10, 05 December 2001).

4. The supplemental information disclosure statement filed on 05 December (Paper No. 8) has been considered.

Claim Rejections - 35 USC § 112

Claims 7, 9-10, 15-17, and 37-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 7, 9-10, 15-17, and 37-38 are directed to a method for treating bradycardia comprising intrapericardial injection of a botulinum toxin to a cardiac muscle by intrapericardial injection to treat bradycardia. The botulinum toxin inhibits the formation or release of the neurotransmitter, acetylcholine, from neurons in the vicinity of the cardiac muscle. The claims also recite that botulinum toxin is botulinum toxin A and is locally administered to the cardiac muscle in an amount between 0.01 U/kg and 35 U/kg, between 0.1 U/kg and 30 U/kg, between 1U/kg and 25 U/kg. The basis for this rejection is set forth for originally filed claims 7-11, 14-18, and 28-34 at pg 4-6 of the previous Office Action (Paper No. 6, 05 July 2001).

Applicant's arguments (Paper No. 10, 05 December 2001), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) It is noted that Applicant has submitted a declaration by John C. Longhurst under 37 CFR § 1.132 (Paper No. 19, 05 December 2001). Applicant asserts that the Longhurst declaration presents admissible expert opinion evidence which rebuts the prima facie case of lack of enablement made by the Office Action and the rejection of the claims under 35 USC §112(1). In the declaration submitted by the Applicant, Dr. Longhurst states that the instant application provides sufficient disclosure so that a cardiologist of ordinary skill can treat bradycardia by

administration of a botulinum toxin into the pericardial space of a human patient. Furthermore, Dr. Longhurst states that "the specific time period in which the toxin should be administered or for how long, and the specific dosage of the botulinum toxin to use entail consideration of factors such as the patient's size, weight, age, and disease severity which factors are routine considerations determined on a patient by patient basis".

Applicant's arguments have been fully considered but are not found to be persuasive. The declaration under 37 CFR 1.132 filed 05 December 2001 (Paper No. 9) is insufficient to overcome the rejection of claims 7, 9-10, 15-17, and 37-38 based upon lack of enablement under 35 U.S.C. §112, first paragraph as set forth in the last Office action (. The declaration is not found to be persuasive because the declarant (Dr. Longhurst) states his position without any scientific reasoning or evidence as to why one skilled in the art would successfully be able to treat bradycardia by administering a botulinum toxin to the pericardial space of a human patient. Therefore, the submitted declaration is an allegation and is insufficient to overcome the rejection of claims 7-11, 14-18, 28-34 (and newly filed claims 37-38) under 35 U.S.C. § 112, first paragraph, enablement.

(ii) Applicant asserts that botulinum toxin has been used therapeutically in many thousands of humans since 1978 to safely and effectively treat different target tissues besides spastic or dystonic muscles, such as pain, inflammatory disorders, excessive sweating, achalasia, anal fissue, and headache. Applicant contends that it is known that the dose of toxin to use by local administration corresponds to the mass of tissue to be treated. Applicant also indicates that the heart is a muscle and the vagal nerve provides cholinergic innervation to the heart. Applicant

asserts that all claims in the instant application are limited to a method for treating bradycardia by intrapericardial injection of a botulinum toxin to a cardiac muscle. Applicant indicates Example 2 of the specification discloses four methods for accessing the pericardial space for intrapericardial administration of a botulinum toxin to treat bradycardia. Applicant argues that the prior art teaches intrapericardial administration of various drugs to humans and therefore, intrapericardial administration of a particular pharmaceutical does not pose any undue or known technical difficulties.

Applicant's arguments have been fully considered but are not found to be persuasive. Although botulinum toxins have been used therapeutically to treat various disorders or conditions, the state of the art is such that no botulinum toxins have been utilized to treat cardiac disorders, such as bradycardia. Furthermore, as discussed in the previous Office Action at pg 5 (Paper No. 6, 05 July 2001), several complications have been associated with botulinum toxin therapy. These challenges include "(a) formation of antibodies and obliteration of response to type-A toxin, (b) lack of alternate botulinum serotypes with the potency and duration of action of type A, (c) diffusion of botulinum toxin to neighboring muscles with transient and sometimes debilitating ptosis, (d) lack of consistency and low specific activities of certain toxin preparations, and (e) the need for repeated injection of toxin in chronic disorders" (Johnson, E. Annu Rev Microbiol 53: 551-575, 1999; pg 566, pp 1).

The specification of the instant application outlines a prophetic procedure for treating bradycardia by intrapericardial injection of a botulinum toxin. However, this is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821

(BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily treat bradycardia by intrapericardial injection of a botulinum toxin to a cardiac muscle. Although the claimed method utilizes routine intrapericardial injection techniques, the results of the method are unpredictable and complex when combined with the step of administering any botulinum toxin.

(iii) Applicant asserts that the present claims are directed to *in vivo* administration of a botulinum toxin directly into the pericardial space. Applicant contends that Lamanna discloses administration of a botulinum toxin systemically and to an isolated (dennervated) heart. Applicant concludes that Lamanna does not disclose or suggest intrapericardial administration of a botulinum toxin. Applicant argues that Lamanna's administration of a botulinum toxin to an isolated heart has no relevance to the claimed invention. Applicant also argues that the specification teaches that the vagus (parasympathetic) nerve innervates the heart and that bradycardia can be treated by the action of a botulinum toxin upon the vagal ending in the heart without any entry of the botulinum toxin in the systemic circulation. Applicant indicates that a proposed mechanism for the efficacy of the present invention is inhibition of vagal activity by intrapericardial administration of a botulinum toxin. Applicant states that down regulation of

vagal activity will permit the unaffected sympathetic innervation of the heart to reduce or eliminate the bradycardia.

Applicant's arguments have been fully considered but are not found to be persuasive. Although Applicant has amended the claims to specifically recite a method of treating bradycardia by intrapericardial injection of a botulinum toxin to the cardiac muscle, the specification of the instant application does not disclose any methods or working examples that administer any botulinum toxin to a cardiac muscle, particularly by intrapericardial injection. There is no guidance in the specification as to the safe dosage and duration of administration of any botulinum toxin to the cardiac muscle. Although the specification discloses ranges of botulinum toxin that could be administered to a patient, depending on weight, size, age, disease severity and responsiveness to therapy (pg 24-26), undue experimentation would be required of the skilled artisan to determine the optimal dose of botulinum toxin to be administered without damage to the heart for every patient. Additionally, there are no methods or working examples in the specification to indicate that intrapericardial administration of botulinum toxin inhibits vagal activity to permit the unaffected sympathetic innervation of the heart to reduce or eliminate the bradycardia, as purported by the Applicant (specification pg 24, lines 7-11 and Response of 05 December 2001, above). Furthermore, Lamanna et al. (Arch Int Pharmacodyn 293 : 69-83, 1988) and Johnson (Annu Rev Microbiol 53: 551-575, 1999) were cited by the Examiner in the previous Office Action (Paper No. 6, 05 July 2001) to establish the state of the art at the time the invention was disclosed. Lamanna et al. and Johnson discuss the challenges of botulinum toxin A therapy and review the unpredictability of the effects of botulinum toxin in a subject. Such complications include "(a) formation of antibodies and obliteration of response to type-A toxin,

(b) lack of alternate botulinum serotypes with the potency and duration of action of type A, (c) diffusion of botulinum toxin to neighboring muscles with transient and sometimes debilitating ptosis, (d) lack of consistency and low specific activities of certain toxin preparations, and (e) the need for repeated injection of toxin in chronic disorders" (Johnson pg 566, pp 1) and "temporary bradycardia and electrocardiographic (ECG) changes" (Lamanna et al. pg 69-70, abstract).

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to determine the dosage and safety of botulinum toxin and the timing and duration of administration, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the prior art (see Johnson and Lamanna et al.), the unpredictability of the effects any botulinum toxin on a subject (see discussion and recited references), undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
February 14, 2002

ELIZABETH C. KEMMERER
PRIMARY EXAMINER